**REMARKS**

The Office Action and cited and applied references have been carefully reviewed. No claim is allowed. Claims 1, 3, 5-12, and 17-25 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

New claim 25 is added and the recited features are supported in the specification on page 12, lines 20-22 and by original claim 14.

Claim 9 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by changing the dependency of claim 9 from claim 1 to claim 3 as helpfully suggested by the examiner.

Claims 1, 8, 11-14, 19, 23, and 24 have been rejected under 35 U.S.C. §102(b) as being anticipated by Sakurai et al. (ref. U1). The examiner states that Sakurai teaches a conjugate of superoxide dismutase and sodium hyaluronate in which the two moieties are covalently linked by a spacer. This rejection is respectfully traversed.

Contrary to the examiner's assertion, the superoxide dismutase (SOD) in the conjugate taught by Sakurai is bound directly to sodium hyaluronate without a spacer. The disclosure in Sakurai of "Conjugation of SOD with sodium hyaluronate" on page 724 shows a reaction of superoxide dismutase with sodium

hyaluronate using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. 1-Ethyl-3-(3-dimethyl aminopropyl) carbodiimide is a catalyst for condensation of carboxylic acids such as sodium hyaluronate with amines such as SOD. It functions by activating the free carboxylic acid of sodium hyaluronate. Attached hereto is page 948 from the reference text, Streitweiser and Heathcock, Introduction to Organic Chemistry, Third Edition, which presents a scheme showing a reaction of carboxylic acid with an amine using a carbodiimide represented by R'N=C=NR'. In the scheme, the intermediate O-acylisourea, which was prepared by reacting the carboxylic acid with the carbodiimide, is shown as an activated carboxylic acid derivative. Nucelophilic substitution of the O-acylisourea by the amine yields the amide and the dialkylurea.

As is clear from the reaction scheme attached hereto, the product of the reaction disclosed in Sakurai is an amide in which amino groups of SOD are directly coupled with carboxylic acid of sodium hyaluronate with no spacer involved. Accordingly, Sakurai cannot anticipate the presently claimed invention where a therapeutic agent for joint diseases is covalently bound to hyaluronic acid via a spacer.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

The examiner has rejected the present claims under 35 U.S.C. §103(a) as being unpatentable over Sakurai as the primary reference in view of one or more secondary references cited and applied in the previous Office Action of February 14, 2003, Paper No. 7, and selected from Gallardy (WO 92/09556), Falk (U.S. Patent 5,910,489), Bemis (U.S. Patent 6,147,080), and Wunderlich (U.S. Patent 6,066,332). The §103(a) rejections are respectfully traversed.

The examiner has acknowledged on page 3 of the present Office Action that the references as applied in the previous Office Action, which include all the secondary references cited and applied in the present Office Action, do not teach or suggest conjugates wherein the therapeutic agent and the hyaluronic acid are covalently bound to each other via a spacer. Therefore, none of the secondary cited and applied references taken alone or in combination with Sakurai and/or with each other can lead one of ordinary skill in the art to the presently claimed invention, given the deficiency in Sakurai as discussed above with regard to the §102(b) rejection.

Furthermore, the conjugate of the present invention has effective pharmacological properties such that the conjugate can be retained in the form of a conjugate at the target site (i.e., a joint cavity) for a long period of time and can exhibit both (1) MMP inhibition as inhibiting the destruction of cartilage

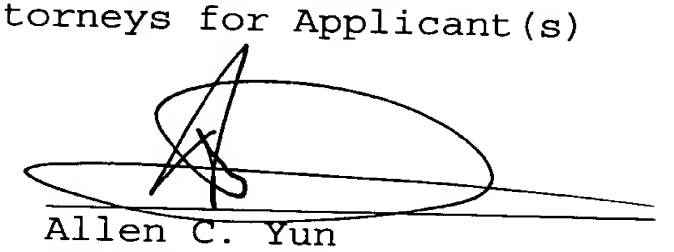
matrix and (2) the medical effect of hyaluronic acids as alleviating the disorder of joint functions by acting as a lubricant, with enhancement of the hyaluronic acid production in joints. See specification at page 5, lines 4-7 and page 7, line 26 to page 8, line 10. The synergistic effects of the presently claimed conjugate as a result of a covalent bond between a therapeutic agent and hyaluronic acid via a spacer is certainly unexpected.

Reconsideration and withdrawal of all the §103(a) rejections are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. 112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By 
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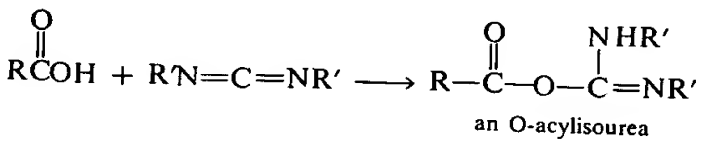
*THIRD EDITION*

# Introduction to Organic Chemistry

*Andrew Streitwieser, Jr.*
*Clayton H. Heathcock*
*UNIVERSITY OF CALIFORNIA, BERKELEY*

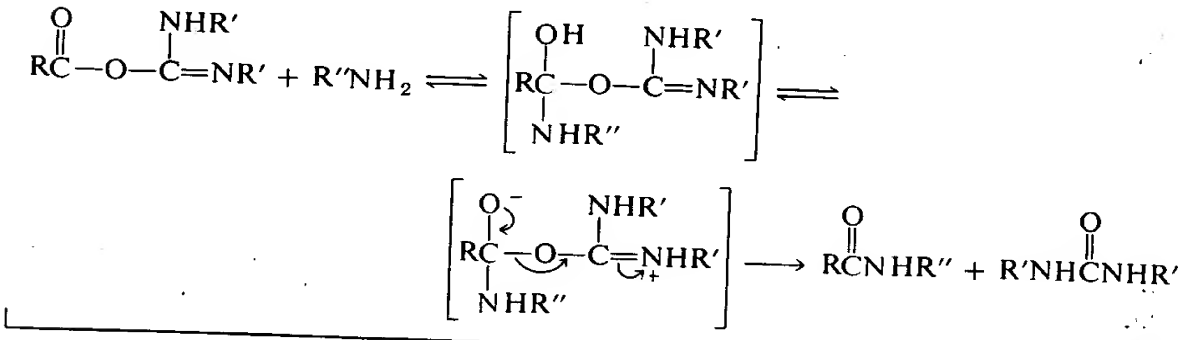
***Macmillan Publishing Company*** *New York*
**Collier Macmillan Publishers** *London*

The probable mechanism for the DCC coupling reaction is outlined as follows. Addition of the carboxylic acid to the diimide gives the ester of isourea, an O-acylisourea.

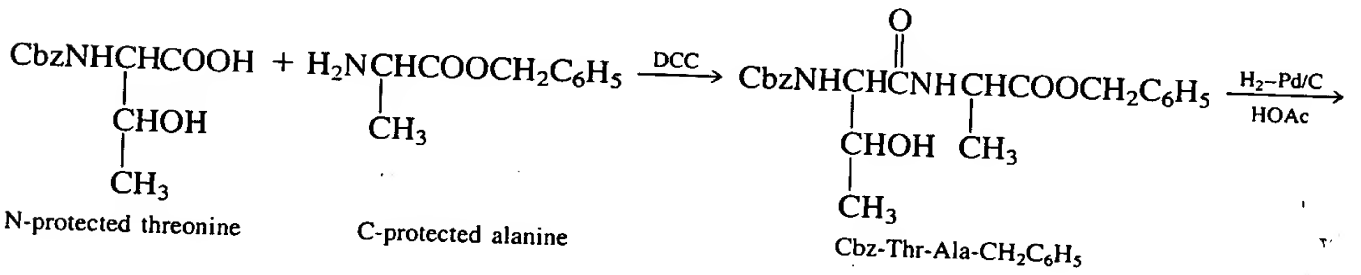


an O-acylisourea

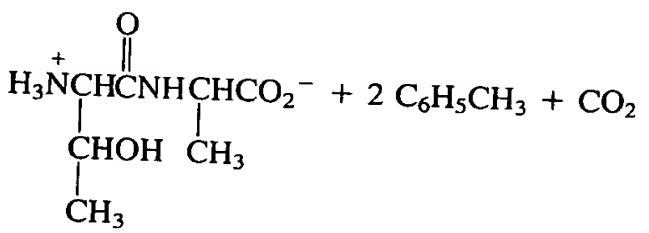
The intermediate O-acylisourea is an *activated carboxylic acid derivative* similar in reactivity to an anhydride or an acyl halide. Nucleophilic substitution by the amine yields the amide and the dialkylurea.



An example of the synthesis of a dipeptide utilizing this method is the synthesis of threonylalanine (Thr-Ala) from benzyloxycarbonylthreonine and alanine benzyl ester.

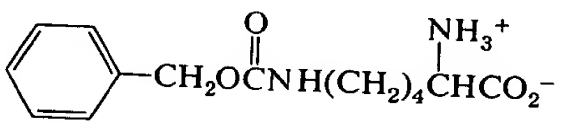


N-protected threonine — C-protected alanine — Cbz-Thr-Ala-$CH_2C_6H_5$

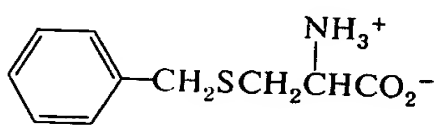


Thr-Ala

Thus far we have discussed peptide synthesis only with amino acids containing no other reactive groups. When there is another functional group present in the molecule, it too must be protected until after the peptide has been formed. Typical protecting groups are benzyloxycarbonyl for the second amino group in lysine and benzyl for the sulfur in cysteine.



ϵ-benzyloxycarbonyllysine



S-benzylcysteine

Both protecting groups are removable by cleavage with anhydrous acids such as hydrogen bromide in acetic acid. The second carboxy group in aspartic acid or glutamic acid is usually protected as a methyl or benzyl ester.